CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057/0

CHEMISTRY REVIEW(S)

Review Date: December 17, 2002

Memo

Ref:	**125057**
Prepared by:	Kurt Brorson, Ph.D., Staff Scientist, DMA\
Through:	Kathleen A. Clouse, Ph.D., Chief, Lab of Cell Biology, DMA Keith Webber Ph.D., Director, DMA
Sponsor:	Abbott
Product:	Adalimumab (Humira)

Background

Abbott has submitted a BLA for adalimumab, an anti-TNF mAb, for use in RA. The following inspections took place related to this BLA:

- Monday, August 19 to Friday, August 23, 2002, Abbott GmbH & Co. K.G. located in Manheim, Germany.
- Abbott Bioresearch Center located in Worcester, MA, Monday, September 9 to Friday, September 13, 2002
- Monday, August 26, 2002 through Tuesday, August 27, 2002 for Labor L + S AG, located in Bad Bocklet, Germany

The following CMC submission have been reviewed by DMA:

- 125057/0 (original submission, 3/28/02)
- 125057/1.0
- 125057 FAX of 9/23/02
- 125057 FAX of 10/9/02
- 125057/0.9

Recommendations:
Based on the pre-approval inspections and DMA's review of the above amendments, DMA recommend approval this BLA including:

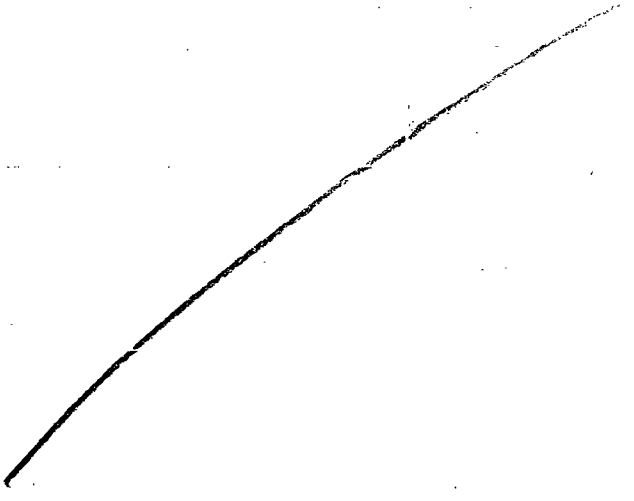
- BDS manufacture at Abbott bioresearch corporation (Worchester MA)
- Drug product manufacture at —
- Final packaging at Abbott (Abbott Park IL)
- The comparability protocol for — process
- The stability protocols for drug substance and drug product.

Review Memo

Ref:	**125057/0.9** (CMC amendment)
Prepared by:	Kurt Brorson, Ph.D., Staff Scientist, DMA
Through:	Kathleen A. Clouse, Ph.D., Chief, Lab of Cell Biology, DMA Keith Webber Ph.D., Director, DMA
Sponsor:	Abbott
Product:	Adalimumab
Date of submission:	October 30, 2002
Review Date:	December 13, 2002

Background

Abbott has submitted a BLA for adalimumab, an anti-TNF mAb, for use in RA. The review of the original submissions raised some CMC issues and an information request letter was sent to the firm on 9/13/02. In this submission, Abbott addresses questions and comments from this letter as well as some concerns raised in previous telecons related to the pre-filled syringes.



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Review Memo

Ref:	**125057/1.0** (CMC amendment)
Prepared by:	Kurt Brorson, Ph.D., Staff Scientist, DMA
Through:	Kathleen A. Clouse, Ph.D., Chief, Lab of Cell Biology, DMA Keith Webber Ph.D., Director, DMA
Sponsor:	Abbott
Product:	Adalimumab
Date of submission:	Sept 4, 2002
Review Date:	**December 7, 2002**

Background

Abbott has submitted a BLA for adalimumab, an anti-TNF mAb, for use in RA. In this amendment, Abbott provides supporting data for:

- Use of a new labeler [redacted] n the [redacted] Abott Park IL) DP finishing facility. This labeler will supplement the [redacted] labeler described in the original submission. Abbott provided the following information to support use of this labeler:
  - Summary comparison of the two labelers [redacted]
  - Description of the labeling process for vials and pre-filled syringes.
  - Equipment validation summary.
  - List of SOPs
  - Facility diagrams.
- Stability data for DS and DP
  - Abbott now has [redacted] of stability data (within specifications @ -[redacted]) for DS lots AFP 06C, 07C, and 08C.
  - Abbott now has [redacted] of stability data (within specifications @ 5°C) for DP vial lots 080100AW, 200AW and 300AW.
  - Abbott now has [redacted] of stability data (within specifications @ 5°C) for DP pre-filled syringe lots 180100AL, 200AL, and 300AL.
- Abbott will add [redacted] as a testing site for pre-filled syringes. This site was inspected by DMPQ as part of the adalimumab BLA review.

Recommendations:

- This submission supports a — expiry for DS and DP vials and an — expiry for pre-filled syringes.

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DATE: December 2, 2002

FROM: Daniel Kearns, HFM-675

THROUGH: Cynthia Kelley, Branch Chief, HFM-675

TO: Dr. Kurt Brorson, HFM-561 Chair Abbott STN 125057
Cc: Craig Doty, RPM, HFM-588; Beverly Conner, HFM-588

SUBJECT: Review of an Abbott amendment 125057/0.9 dated October 30, 2002 in response to a CBER information request. There are a number of issues addressed in the Abbott response, but this review is only for the addition of — as an alternate site for packaging/labeling of Adalimumab.

CONCLUSION: The information procedures, controls, and data appear satisfactory, and therefore I recommend approval of — as an alternate packaging/labeling site for Abbott's Adalimumab.

REFERENCES
FEDERAL REGISTER, Vol. 58, No 147, Tuesday, August 3, 1993, Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Revision of Certain Labeling Controls, page 41348.

BACKGROUND
Abbott Laboratories has submitted an application (986 total jackets, i.e., volumes in paper and electronic form) for Adalimumab (trade name to be determined), which is a human recombinant IgG antibody directed against human tumor necrosis factor-alpha for the treatment of rheumatoid arthritis.

Amendment 125057/0.9, dated October 30, 2002 and received by myself on November 15, 2002 is a response to further CMC questions/comments from CBER regarding sundry CMC questions, e.g., tracking of addition stability parameters, additional validation after — the addition of — as a alternate packaging/labeling site, and additional information regarding the use of — as a packaging component for the product. In tab 10, page 384, it is also noted that release of the final labeled vials of Adalimumab from Abbott GmbH & Co. KG. However, as the Abbott GmbH location already receives, tests, and releases Adalimumab in unlabeled syringes, the addition of release responsibility of final labeled syringes is minor. This review only evaluates Abbott's request for — as an alternate labeling/packaging location for Adalimumab.

In an e-mail string culminating in an e-mail dated November 22, 2002 at 2:41 pm, documenting a telecon between myself and Abbott representatives, I (DK) delineated the information that would be needed to approve Abbott's request to use — as an alternate labeler/packager (see attached e-mail).

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Review Memo

Ref: **125057**

Prepared by: Kurt Brorson, Ph.D., Staff Scientist, DMA

Through: Kathleen A. Clouse, Ph.D., Chief,
Lab of Cell Biology, DMA
Keith Webber Ph.D., Director, DMA

Cc:

Sponsor: Abbott

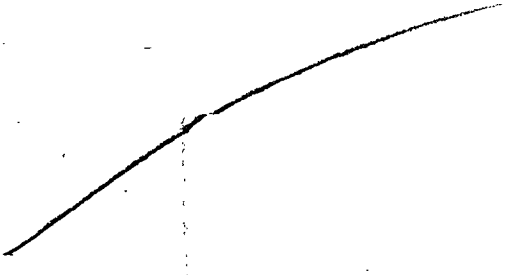
Product: Adalimumab

Date of submission: October 22, 2002

Review Date: October 23, 2002

Background

Abbott submitted a BLA for Adalimumab, an anti-TNF mAb for RA. Abbot was contacted on Oct 3, 2002 and asked a question regarding their FAX of Sept 26, 2002. "Please set stability specifications for



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DATE: October 22, 2002

FROM: Daniel Kearns, HFM-675

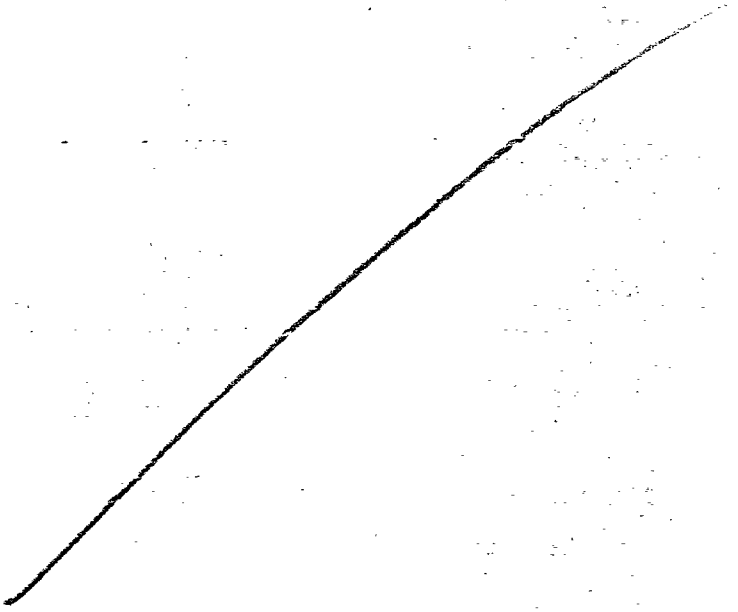
THROUGH: Cynthia Kelley, Branch Chief, HFM-675

TO: Beverly Conner, RPM, HFM-588; cc Dr. Kurt Brorson, HFM-561

SUBJECT: Review of IND 7627, amendment number 388 dated September 30, 2002 for a new scale — for manufacture of the drug substance Adalimumab (for treatment of rheumatoid arthritis). NOTE: the firm's submission states this is serial number 385.

CONCLUSION: This additional information received at CBER on September 19, 2002 to Abbott's STN 125057 submission appears satisfactory.

BACKGROUND:
This submission, received by myself on October 10, 2002, provides information on the manufacturing of Adalimumab (D2E7) drug substance at the — scale. In a pre-BLA meeting held on October 30, 2001, the Agency agreed that one inspection at the time of the pre-approval inspection (at — scale) for Adalimumab would suffice if manufacturing data was available for review at the — scale during the inspection. Also, a Type C meeting was held between CBER and Abbott about the — for manufacture at the — scale on June 22, 2000. The inspection of the Worcester, Massachusetts site was conducted from September 9 to 13, 2002 and was classified as VAI (4 observations). Procedures, controls, and raw data was reviewed during the inspection and found satisfactory. This submission provides information on the:



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DATE: October 15, 2002

FROM: Daniel Kearns, HFM-675

THROUGH: Cynthia Kelley, Branch Chief, HFM-675

TO: Craig Doty, RPM, HFM-588

SUBJECT: Review of a response dated September 16, 2002 for additional information from Abbott Laboratories for BLA STN 125057 Adalimumab (D2E7) (for treatment of rheumatoid arthritis)

CONCLUSION: This additional information received at CBER on September 19, 2002 to Abbott's STN 125057 submission appears satisfactory.

BACKGROUND

Abbott Laboratories and has submitted an application (986 total jackets, i.e., volumes in paper and electronic form) for Adalimumab (trade name to be determined), which is a human recombinant IgG antibody directed against human tumor necrosis factor-alpha for the treatment of rheumatoid arthritis.

In an e-mail dated Friday, June 14, 2002 at 9:33 am, Ms. Conner (RPM for this submission) informed a number of reviewers and their supervisors that Abbott had sent in correspondence (dated June 7, 2002) requesting advice on whether the submission of an amendment would impact the review timeframes (i.e., negatively). The amendment would be for a new labeler at Abbott Park, Illinois. The Abbott Park location is the location currently described in the BLA for labeling operations. The June 7, 2002 request described the circumstances, and provided schematics of the current and proposed areas with the new labeler.

In an e-mail dated June 14, 2002 at 1:30 pm, I responded to Ms. Conner (as well as my supervisor and number of involved individuals) about the affect that a new labeler would have on the review clock. I stated that reviews of labeling equipment are relatively easy as the regulations on labeling controls are numerous and straight forward, making the review relatively easy, and recommended that the submission of such an amendment would not delay my review.

REVIEW

This submission to Abbott's STN 125057/0 is dated September 16, 2002, was received at CBER on September 19, 2002, and was received by myself on September 26, 2002. The submission is divided into 8 tabs. Each tab is reviewed separately below.

_____ This section provides information for an alternate labeler to be used for labeling of pre-filled syringes in building — at the Abbott Park location in Illinois. The original information on the application of the physical label onto the final container

was addressed in volume 9, page 356. This submission describes the room, controls, and flows of material during labeling operations. The relocation of the previous labeling equipment to a new room is also described. A summary of the various validation documents is provided. There are 26 qualification or validation report titles provided. The documents include the labeler/(syringe) system, various software, utilities, and A listing of standard operating procedures is also provided. I note that this site , and has been FDA inspected.

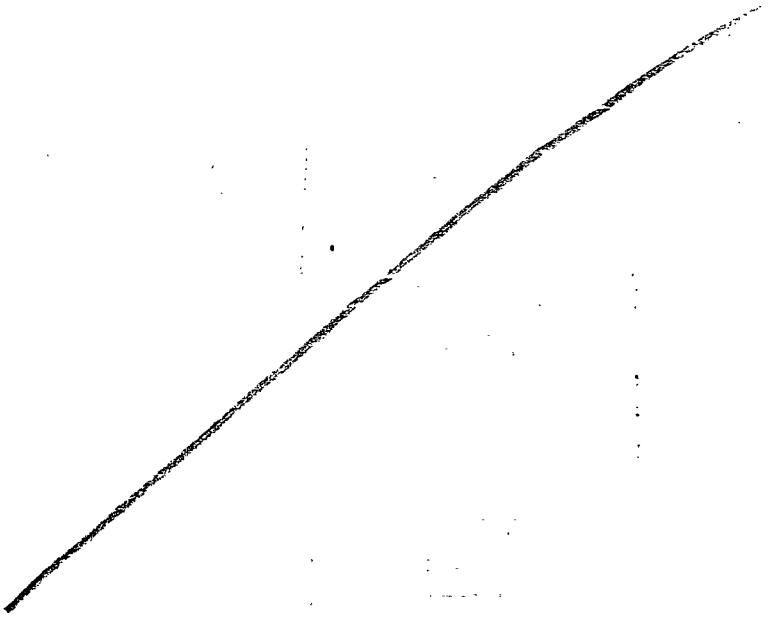
Stability Update Drug Substance This section provides updated data from the ongoing stability studies for the drug substance. All data submitted, except in some instances for the accelerated stability data at high temperatures, met specifications.

Stability Update Pre-filled Syringe This section provides updated stability data, and again all specifications, except some instances under accelerated conditions, met acceptance criteria.

Stability Update Pre-filled Syringe This section contains updated stability data from the ongoing studies for the pre-filled syringe, and again all specifications, except some instances under accelerated conditions, met acceptance criteria.

. Test Site This merely updates the listing of contract manufacturing sites is now authorized to do The list updates the site for the additional testing of the pre-filled syringes.

Drug Substance Batch Records



Master Batch Record This is a listing of minor changes to the batch record used at [redacted] and updates the documents submitted in volume 8, page 72 of the original CMC submission. Basically, the changes consist of [redacted] The additions appear non-substantive and appropriate.

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ON ORIGINAL

Review Memo

Ref:	**125057/0**
Prepared by:	Kurt Brorson, Ph.D., Staff Scientist, DMA
Abbott:	Becky Welch
Product:	Adalimumab
Date:	FAX of 10/9/02
Review Date:	October 9, 2002

Background

Abbott submitted a BLA for Adalimumab, an anti-TNF mAb for RA. Abbot was contacted on 10/4/02 and asked if the safety device with needle stick features on the hospital pack pre-filled syringes was approved under 510K.

In this FAX of 10/9/02, Ms. Welch replied that the safety device with needle stick features on the hospital pack pre-filled syringes was is an [redacted] needle guard purchased from [redacted] The 5/10K number for this device is [redacted]

Recommendation: This resolves the issue concerning approval of the safety device with needle stick features.

Review Memo

Ref:	**125057/0**
Prepared by:	Kurt Brorson, Ph.D., Staff Scientist, DMA
Through:	Kathleen A. Clouse, Ph.D., Chief, Lab of Cell Biology, DMA Keith Webber Ph.D., Acting Director, DMA
Cc:	Sheldon Kress, Jeff Siegel DCTDA
Sponsor:	Abbott
Product:	Adalimumab
Date of submission:	FAXed 9/23/02
Date of review:	Oct 3, 2002

Background

Abbott submitted a BLA for Adalimumab, an anti-TNF mAb for RA.

As part of the BLA review, Abbot was contacted on 9/23/02 and asked two specific questions:

1) Is the syringe used to deliver DP an approved device? Is there a 510K?
   Ans: The syringe system, purchased from [redacted], is regulated as a container closure system, not as a device.

2) Regarding the [redacted] immunogenicity rate stated in the package insert (PI):
   a) What is the denominator that was used to calculate this? **Ans**: The denominator is [redacted] These patients were in three clinical trials, DE011, DE009 and DE019.

b) Is the reported rate from the new, tween-containing formulation? **Ans:** no, none of the patients in these three trials received the new formulation. **Note:** Abbott should commit to revising the rate stated in the PI when immunogenicity data becomes available from patients treated with the new formulation.
c) Please provide a breakdown into those patients receiving MTX and those on single therapy. The MTX rate is 1%; the rate without MTX is 11.5%.

Recommendation:

Follow up on the following items:

- Contact Abbott and ask for the information suggested by Viola Hibbard.
- Obtain a commitment regarding revising the rate stated in the PI when immunogenicity data becomes available from patients treated with the new formulation.
-

DATE: October 1, 2002

TO: STN 125057/0 file

FROM: Daniel Kearns, HFM-675

SUBJECT: Abbott Laboratories' request for Categorical exclusion under 21 CFR 25.31(c)

I have reviewed the pertinent section (Chemistry Review Volume 10, section 4.6, page 317) of the Biologics License Application (STN 125057/0) from Abbott Laboratories (license number 43) for Adalimumab (CHO cell derived recombinant human TNF antibody), and find that their request for a categorical exclusion from an environmental assessment under 21 CFR 25.31(c) is justified as the product is composed of naturally occurring substances, and that no extraordinary circumstances exist.

_____ _____

Date

Daniel Kearns
CMC reviewer

Concurrence:

_____ _____

Date

John A. Eltermann, Jr., R.Ph., M.S.
Director
Division of Manufacturing Product Quality

This memo prepared in accord with SOPP8401.2
Dated July 26, 2002
Section 6.C.vi.b

DATE: September 30, 2002

FROM: Daniel Kearns, HFM-675

THROUGH: Cynthia Kelley, Branch Chief, HFM-675

TO: Ms. Beverly Conner, RPM, HFM-588

SUBJECT: Review of Abbott Laboratories' BLA STN 125057 Adalimumab (D2E7) for treatment of rheumatoid arthritis.

CONCLUSION: The submission appears to have provided all information in accord with CBER's CMC guidance document for a specified biotechnology product. The data, procedures, and controls support the conclusion that the product can consistently be manufactured meeting its predetermined quality attributes.

BACKGROUND

Abbott Laboratories and has submitted an application (986 total jackets, i.e., volumes in paper and electronic form) for Adalimumab (trade name to be determined), which is a human recombinant IgG antibody directed against human tumor necrosis factor-alpha for the treatment of rheumatoid arthritis. NOTE: The applicant states that throughout the submission the sponsor may be referred to as BASF, Knoll Pharmaceutical, or Abbott Laboratories. This is due to Abbott's acquisition of Knoll Pharmaceuticals from BASF, which occurred during the development of data and information in March, 2001 for this BLA.

The index discloses that the CMC information is in jackets 4 through 20. NOTE: Abbott uses the term "Jacket" to refer to volumes in sequential order, i.e., jacket 1 of 986, while volumes are sequentially numbered by topic, e.g., clinical, chemistry, etcetera - - Chemistry Review volume 10 of 17 corresponds to jacket 13 of 986. I have in my possession CBER review copy 2 of Chemistry volumes 1 - 17 (jackets 4 - 20 of 986) and copy 3 of Summary review volumes 1 - 3 (jackets 1- 3). (NOTE: this is substantially different than the DCC routing slip which states that I have volumes 18 through 34 and 7 through 9 which does not correspond to the chemistry review volumes I have or the jackets).

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Review Memo

Ref:	**125057/0**
Prepared by:	Kurt Brorson, Ph.D., Staff Scientist, DMA
Through:	Kathleen A. Clouse, Ph.D., Chief, Lab of Cell Biology, DMA Keith Webber Ph.D., Acting Director, DMA
Sponsor:	Abbott
Product:	Adalimumab (USAN); D2E7 (lab name); brand name not yet assigned
Date of submission:	March 28, 2002
Date of review:	June 26, 2002

Background

Abbott has submitted a BLA for adalimumab, a phage display anti-TNF mAb for use in RA patients. DS is produced by CHO cell culture at Abbott BioResearch Center, Worchester MA. DP, 0.8 ml of a 50 mg/ml solution, will be marketed in vials [redacted] or prefilled syringes

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DATE: May 2, 2002

FROM: Daniel Kearns, HFM-675

THROUGH: Cynthia Kelley, Branch Chief, HFM-675

TO: Ms. Beverly Conner, RPM, HFM-588

SUBJECT: Filing review of Abbott Laboratories' BLA STN 125057 Adalimumab for treatment of rheumatoid arthritis.

CONCLUSION: The submission appears to meet the filing criteria from a CMC review standpoint.

BACKGROUND: Two CBER documents were used as guidance in evaluating this submission for filing. The first is SOPP 8404, (1/20/00) "Refusal to File Guidance for Product License Applications and Establishment License Applications." The second CBER document was "Guidance for Industry For the Submission of Chemistry, Manufacturing, and Controls information For a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product For In Vivo Use (August, 1996).

Abbott Laboratories and has submitted an application (986 total jackets, i.e., volumes in paper and electronic form) for Adalimumab (trade name to be determined), which is a human recombinant IgG antibody directed against human tumor necrosis factor-alpha for the treatment of rheumatoid arthritis.

The index discloses that the CMC information is in jackets 4 through 20. NOTE: Abbott uses the term "Jacket" to refer to volumes in sequential order, i.e., jacket 1 of 986, while volumes are sequentially numbered by topic, e.g., clinical, chemistry, etcetera - - Chemistry Review volume 10 of 17 corresponds to jacket 13 of 986. I have in my possession CBER review copy 2 of Chemistry volumes 1 - 17 (jackets 4 - 20 of 986) and copy 3 of Summary review volumes 1 - 3 (jackets 1- 3). (NOTE: this is substantially different than the DCC routing slip which states that I have volumes 18 through 34 and 7 through 9 which does not correspond to the chemistry review volumes I have or the jackets).

The bulk manufacturing facility is located in A complete listing of the filling (two filling sites - one for vials, one for syringes and are both located in and various testing laboratories is provided with the form FDA 356h(4/00), as well as being described in more detail in applicable portions of the submission.

Form 356h (4/00) is submitted and appears to address all appropriate points. The environmental assessment is in jacket 13, page 317, in which the firm request a categorical exclusion under 21 CFR 25.31(c). Jacket 1 lists clinical investigators

(physicians) who participated in the studies supporting this application and certifies that no financial arrangements have been made where the compensation to the investigator could be affected by the outcome of the study as defined under 21 CFR 54.2(a), (b), and (f).

Jacket 1 (summary review volume 1 of 3) contains the CMC table of contents. The index provides sections for the drug substance addressing the structure, description of [redacted] system, descriptions of the various manufacturing processes, facilities, [redacted] studies, manufacturing process validation, container/closure systems, and stability reports. A summary of the in-process tests is included. Analogous details for the drug product are also provided in the table of contents.

Summary volume 2 (jacket 2) contains package insert and labeling information.
Summary volume 3 (jacket 3) provides sundry data regarding non-clinical pharmacology and toxicology, statistical analysis, etcetera.

Chemistry Volume 1 (jacket 4) contains information on the description and characterization of the drug substance, as well as facility descriptions.

Chemistry Volume 2 contains an overview of the manufacturing process, [redacted], etcetera is also described here.
Chemistry Volume 3 contains blank batch records.
Chemistry Volume 4 contains executed batch records.
Chemistry Volume 5 contains various process documents, including validation protocols, analytical method descriptions, stability data, etcetera.
Chemistry Volume 6 also contains a wide variety of documents, among them [redacted] validation.
Chemistry Volume 7 consists of a wide variety of information regarding specifications.
Chemistry Volume 8 consists of information regarding the drug product in pre-filled syringes.
Chemistry Volume 9 consists of a variety of information regarding validation of the manufacturing processes associated with the pre-filled syringes.
Chemistry Volume 10 consists of information regarding specifications and test methods for drug product.
Chemistry Volume 11 consists of information related to drug substance QC methods and validation.
Chemistry Volume 12 consists of additional information related to drug substance QC methods and validation as well as drug product.
Chemistry Volume 13 consists of data related to [redacted]
Chemistry Volume 14 consists of more test data from various validation protocols.
Chemistry Volume 15 consists of more test data from various validation protocols, e.g., [redacted]

Chemistry Volume 16 consists of protocols and results for the validation of the [redacted]

Chemistry Volume 17 consists of protocols and results for the evaluation of the [redacted] with regards to [redacted]

Cc:
Dr. Kurt Brorson

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ON ORIGINAL